CORRESPONDENCE

Intravenous Iron and Maintenance Hemodialysis

TO THE EDITOR: In the Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial conducted by Macdougall et al. (Jan. 31 issue),[1] the reactive, low-dose iron regimen (in which intravenous iron was administered if the ferritin concentration was <200 μg per liter or the transferrin saturation was <20%) resulted in iron deficiency anemia and harmed the patients. Nearly half the patients had a transferrin saturation of less than 20%, and approximately 25% of the patients had a serum ferritin concentration of less than 100 μg per liter. This culminated in persistent thrombocytosis and a drop in the hemoglobin level. Despite the protocol mandating that the hemoglobin level be maintained between 10 and 12 g per deciliter with the administration of an erythropoietin-stimulating agent, nearly 25% of the patients had a hemoglobin level of less than 10 g per deciliter in the first 9 to 12 months of the trial.

The drop in hemoglobin levels resulted in a higher incidence of transfusion, as well as a higher incidence of recurrent cardiovascular events, in the low-dose group than in the high-dose group. Whereas the median dose of erythropoietin-stimulating agent did not decrease in the high-dose group, it increased in the low-dose group. The between-group difference in the median dose of erythropoietin-stimulating agent was therefore due to increased use in the low-dose group. These data suggest that iron deficiency anemia in patients undergoing hemodialysis results in the increased use of erythropoietin-stimulating agents and transfusions and an increased incidence of recurrent heart-failure events.

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Dr. Agarwal reports being a member of data and safety monitoring committees for AstraZeneca and Ironwood Pharmaceuticals, of steering committees for randomized trials for Akebia Therapeutics, Bayer, Janssen, GlaxoSmithKline, Relypsa, Sanofi, and Genzyme, of adjudication committees for Bayer, Boehringer Ingelheim, and Janssen, and of scientific advisory boards for Relypsa and Reata Pharmaceuticals and receiving consulting fees from Bird Rock Bio, Celgene, Daiichi Sankyo, Eli Lilly, Takeda Pharmaceutical, and ZS Pharma. No other potential conflict of interest relevant to this letter was reported.

1. Macdougall IC, White C, Anker SD, et al. Intravenous iron in patients undergoing maintenance hemodialysis. N Engl J Med 2019;380:447-58.
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TO THE EDITOR: Macdougall et al. report the highly anticipated results of the PIVOTAL trial, which showed that the use of erythropoiesis-stimulating agents and blood transfusions was substantially lower with a high-dose iron sucrose regimen than with a low-dose iron sucrose regimen in patients undergoing hemodialysis. The trial showed the noninferiority of the high-dose regimen to the low-dose regimen with respect to the risks of death, major adverse cardiovascular events, and infection. However, we would like to emphasize that currently, at least in the Netherlands, the use of iron sucrose is no longer daily practice, since nearly all dialysis centers have switched to newer (and generally considered to be better) intravenous iron preparations, such as ferric carboxymaltose or iron isomaltoside.[1-3]

Recently, our group found that switching from iron sucrose to ferric carboxymaltose in patients undergoing hemodialysis resulted in improved iron status and hemoglobin levels and less use of erythropoiesis-stimulating agents in patients who were administered less iron.[4] Hence, we anticipate that by using newer intravenous iron preparations, the currently major identified results (i.e., use of lower doses of erythropoiesis-stimulating agents and fewer blood transfusions) will be more apparent.

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Dr. Eisenga reports receiving speaking fees from Vifor Pharma, and Dr. Gaillard, receiving speaking fees and research funding from Vifor Pharma, serving on advisory boards for Vifor Pharma, Amgen, Roche, and Pharmacosmos, and being a member of the FIND-CKD (Ferinject Assessment in Patients with Iron Deficiency Anaemia and Non-Dialysis-Dependent Chronic Kidney Disease) trial steering committee. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In their article, Macdougall et al. seem to claim that, in patients undergoing hemodialysis, intravenous iron administration at a high dose is safe and is associated with lower doses of erythropoiesis-stimulating agent than a low iron dose in patients undergoing hemodialysis. In our view, the authors merely found no significant differences in the risks of death, major cardiovascular events, and infection between the high-dose group and the low-dose group. However, a substantial amount of iron was administered, even in the low-dose group. One could conclude that the risk associated with intravenous iron is the same among patients whose ferritin concentrations are more than 100 to 200 μg per liter as it is among patients with renal anemia who are undergoing hemodialysis. In an observational study, we found that patients with a higher ferritin concentration (≥100 μg per liter) had a higher risk of cardiovascular and infectious diseases than patients with a lower ferritin concentration (<100 μg per liter).[1] We would like to remind readers that high ferritin concentrations are associated with a rise in the hepcidin level, which could hamper iron reutilization and induce hyporesponsiveness to erythropoiesis-stimulating agents.[2] Given the threshold for ferritin concentration for these risks, it would be useful to explore well-balanced therapy with erythropoiesis-stimulating agents and iron for the treatment of renal anemia.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The trial by Macdougall et al. compared the administration of high-dose iron sucrose with low-dose iron sucrose in patients undergoing hemodialysis. Patients in the high-dose group underwent fewer blood transfusions and received lower doses of erythropoiesis-stimulating agents to maintain target hemoglobin levels than those in the low-dose group. The two groups were well balanced in various aspects. However, the use of angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) was lower in the high-dose group than in the low-dose group (276 of 1093 patients [25.3%] vs. 318 of 1048 patients [30.3%], P=0.009).

Although this trial is informative, we think that different use of ACE inhibitors and ARBs may have effects on the results. Although the idea is not universally accepted, studies have shown that the use of ACE inhibitors or ARBs is associated with anemia in patients with chronic kidney disease.[1-3] The use of ACE inhibitors and ARBs may be a component of hyporesponsiveness to erythropoiesis-stimulating agents in patients with chronic kidney disease.[4] Therefore, we would suggest that the low use of erythropoiesis-stimulating agents and low incidence of transfusion may be attributable in part to the low percentage of patients who used ACE inhibitors and ARBs. We think that it would be better if the analysis had been adjusted for the use of ACE inhibitors and ARBs.

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THE AUTHORS REPLY: Given the global variation in the use of intravenous iron in routine practice,[1] it is enlightening to receive perspectives from the United States, the Netherlands, Japan, and Turkey, particularly the opposing views from the United States and Japan. These views reflect the extremes of iron use worldwide.[1]

We agree with Agarwal that many patients in the low-dose group of the trial had borderline or overt iron deficiency, which was harmful. However, the ferritin and transferrin saturation thresholds for iron administration in this group were consistent with European guidelines[2] and exceeded the recommendations from Japan,[3] even though many physicians in the United States adopt iron-management strategies that are consistent with those in the high-dose group. Recently, Agarwal expressed concerns about exacerbating cardiovascular events and infections with intravenous iron[4]; perhaps the results of our trial have induced reconsideration on this point.

The claim by Eisenga et al. that the use of newer intravenous iron preparations may produce positive outcomes similar to those seen in our trial with a less pronounced high-dose regimen may be true. However, in the absence of randomized, controlled trials, such claims should be tempered.

Nakanishi and Kuragano comment that patients in the low-dose group still received a "substantial amount of iron," which may be true by Japanese standards but is certainly not the case for the rest of the world[1] and is inconsistent with the comments of Agarwal (see above). Furthermore, we suggest that the concern of Nakanishi and Kuragano that the risks of cardiovascular and infectious complications with intravenous iron above a range of ferritin concentration of 100 to 200 μg per liter, as compared with less than 100 μg per liter, seems misguided, given that this concern is based on observational data.

Afsar and colleagues suggest that our analysis should be adjusted because of a significant difference in the baseline use of ACE inhibitors and ARBs. First, we note that post hoc adjustment for imbalances in baseline characteristics can lead to biased estimation of treatment effects and is not a recommended approach, as explained by the late Doug Altman.[5] The adjusted analysis for our primary end point provides an estimated hazard ratio of 0.83, with a 95% confidence interval of 0.71 to 0.97, and a P value for superiority of 0.02 for the comparison of the proactive, high-dose iron regimen with the reactive, low-dose regimen. However, we would urge readers to ignore this apparently improved result and to focus on the results that were based on our prespecified analysis strategy.

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Since publication of their article, the authors report no further potential conflict of interest.

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